AmpliChip CYP450 Test: personalized medicine has arrived in psychiatry

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The US FDA has granted market approval for the first pharmacogenetic test using a DNA microarray, the AmpliChip CYP450, which genotypes cytochrome P450 (CYP)2D6 and CYP2C19. The test uses software to predict phenotypes and tests for 27 CYP2D6 alleles, including the deletions and duplications, and three CYP2C19 alleles. Other DNA microarray platforms are being developed for CYP testing, but none have been completely developed or approved by the FDA to date. The differences between an implementation of pharmacogenetic tests centered on the individual and implementation using a public health approach are discussed. In this review, the major obstacles to the wide implementation of pharmacogenetic testing in the clinical environment are summarized.

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Two interwoven processes – human genome sequencing and the development of new technologies permitting genetic testing in an automated and efficient manner – have led to the so-called genetic or genomic revolution. The development of genomic medicine and genetic testing has helped in the diagnosis of some relatively rare and unusual disorders, but this has had limited impact in medicine. On the other hand, the field of pharmacogenetics or pharmacogenomics may be the potential driving force for implementing genetic medicine in primary care. Pharmacogenetics is usually defined as the study of variability in drug response due to heredity. More recently, the term pharmacogenomics has been used, a broader term encompassing all genes in the genome that may determine drug response. The distinction is arbitrary. Both terms are used interchangeably and lay journals prefer to use a broader term; personalized or individualized prescription. In 1997, the journal *Science* described 'personalized prescription' or 'tailoring drugs to a patient's genetic makeup' and predicted that it will 'soon' reach clinical practice. According to the lay journal *Time* (1999), the more precise definition for 'soon' was 2015, and according to the *Journal of the American Medical Association* (2001), it was 2020.

In December 2004, the US FDA granted market approval for the first pharmacogenetic test using a DNA microarray, the AmpliChip CYP450 Test (Roche Molecular Systems, Inc.) [101], through its Office of *In Vitro* Diagnostic Device Evaluation and Safety [1]. This test performs massive parallel genotyping using the GeneChip® System 3000Dx microarray platform (Affymetrix, Inc.) [102]. The AmpliChip CYP450 Test assesses two polymorphic genes; cytochrome P450 (CYP)2D6 and CYP2C19. As CYP2D6 metabolizes many of the psychiatric drugs (antipsychotics and antidepressants), psychiatry has become the first area of medicine where pharmacogenetic testing using DNA microarrays is available. Due to this twist of fortune, a recent article in *Business Week* focused on personalized medicine, and described the potential for personalized medicine in a psychiatric patient [2].

CYP2D6 is a metabolic liver enzyme that metabolizes approximately 25% of drugs known to be metabolized by CYPs [3]. The CYP2D6 enzyme is expressed constitutively in several tissues, in particular the liver, and thus, the type of CYP2D6 alleles expressed in a subject primarily defines enzyme activity. CYP2D6 cannot be induced [4]; therefore, intake of CYP2D6 inhibitors is the only significant

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environmental factor that can possibly modify CYP2D6 activity. This makes CYP2D6 genotyping a good candidate for pharmacogenetic testing. The smaller the impact environmental influences have on a metabolic enzyme, the easier it should be to detect the effects of a genetic polymorphism [5]. The activity of the CYP2D6 enzyme is extremely variable due to more than 90 genetic variations, and can be expressed as four main levels of activity (or phenotypes): ultrarapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM) [6]. In the traditional view, a UM subject has three or more copies of the active CYP2D6 gene and exhibits extremely high CYP2D6 activity. The prevalence of UMs is approximately 5% in European Caucasians (1% in northern Europe and 10% in southern Europe), 4.5% in African–Americans and up to 29% in North Africa and the Middle East [5]. The normal subject, or EM, has one or two functional copies of the CYP2D6 gene and displays typical CYP2D6 activity. The AmpliChip CYP450 Test defines an IM as a subject with one nonfunctional CYP2D6 allele and an allele that is expressed as an enzyme with low activity [6,7], but other groups consider subjects with one functional copy of CYP2D6 as IM rather than EM [8]. In reality, with our currently limited knowledge, this distinction between IMs and EMs is more important for researchers than for clinicians, since its clinical relevance must be demonstrated. Without doubt, the most important phenotype is the PM, which is associated with two nonfunctional CYP2D6 alleles and no CYP2D6 enzyme activity in their liver. Approximately 7% of Caucasians and 1–3% of other races are PMs. There are two main CYP2C19 phenotypes: a majority of normal (EM) subjects and PMs (up to 25% in East Asians and 1–5% in other races) [5].

Traditional testing methods versus the AmpliChip CYP450 Test

Traditionally, most genotype assays were conducted in research laboratories and used PCRs to amplify the DNA, coupled with various post-PCR detection methods [9]. Two major weaknesses of these methods are that each sample needs to be repeatedly tested for each polymorphism found in a given allele, and that the normal allele (wild-type allele, termed *1) is assumed by default. Therefore, a laboratory testing too few inactive CYP2D6 alleles will erroneously classify PMs as EMs (false negatives for PMs). To test for each of the more than 90 known genetic variations of CYP2D6 using these traditional methods would require testing each sample more than 90 times, a very inefficient method [103]. Some of the CYP2D6 and CYP2C19 alleles are very rare and new ones are being discovered every year; thus, it may not be cost-effective to screen for them in the average subject. There is no agreement on how many CYP2D6 alleles constitute the minimum number that should normally be tested, but approximately 15–25 are relatively frequent in one of the major racial groups. A recent article has proposed testing 24 CYP2D6 alleles (*1, *1xn, *2, *2xn, *3, *4, *4xn, *5, *6, *9, *10, *8/14, *17, *21, *29, *35, *35xn, *36, *40, *41, *42, *43, *45 and *46) [10]. Two major mutations (*2 and *3) explain almost all cases of CYP2C19 PMs [11].

The AmpliChip CYP450 microarray contains over 15,000 oligonucleotide probes, thereby enabling testing for 20 CYP2D6 alleles (*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *19, *20, *29, *35, *36, *40 and *41), seven CYP2D6 duplications (*1xn, *2xn, *4xn, *10xn, *17xn, *35xn and *41xn), and three CYP2C19 alleles (*1, *2 and *3) [12]. Compared with traditional methods, the AmpliChip CYP450 Test has the advantage of not relying on the identification of a normal allele by default. It has wild-type and mutant probe sets; thus, it queries directly for either the wild-type or mutant sequence. The inclusion of software using algorithms to predict the CYP2D6 and CYP2C19 phenotypes is another major advance. The initial steps of the AmpliChip CYP450 Test are similar to the traditional methods and involve PCR amplification of selected DNA segments, followed by application of the fragmented, labeled DNA to the microarray for hybridization and staining, laser scanning of fluorescent hybridization intensity pattern, and then software interpretation of the genotype and phenotype [7,9,12,13].

According to the manufacturer, the lowest DNA input required to obtain a correct genotype with at least 95% positive rate is 25 ng for CYP2D6 and 2.5 ng for CYP2C19 [7]. At first glance, this number appears to be irrelevant for clinicians, but actually it has major practical implications. In the past, a blood collection was used to complete the CYP2D6 genotype. The AmpliChip CYP450 Test's low DNA detection limit remarkably simplifies the process, enabling the use of buccal swabs to collect DNA. DNA collection is similar to brushing the cheek with a toothbrush, and is more readily accepted by patients than venipuncture. In the author's experience, the buccal swab is also easier to mail to genotyping laboratories if needed [12]; however, Roche recommends the use of blood when genotyping patients with the AmpliChip CYP450 Test [7]. Recently, a new saliva kit has become commercially available and registered with the FDA [104]. Although the author has no experience using this kit, it appears very promising.

Two major cost determinants are the equipment and the use of one DNA chip for each DNA sample tested (each AmpliChip CYP450 Test is discarded after being used) (TABLE 1). It is estimated that a laboratory with expertise could complete the test in 8 h from sample preparation to genotype determination [13,14]. Several US laboratories offer the test (TABLE 1) [105–108].

Sensitivity & specificity

Sensitivity is the true positive rate, specificity is the true negative rate and accuracy consists of the true positives and true negatives as a proportion of all results [15]. At first glance, defining the sensitivity and specificity of this test should be simple. However, the author can think of at least three levels of sensitivity and specificity: the mutant versus non-mutant allele distinction; detection of each phenotype; and a phenotype to make clinical predictions. As this is a new field, it is not surprising that the information on these three levels is very limited.

In 232 volunteers, five CYP2D6 alleles (*3, *4, *6, *7 and *9) were tested by both allele-specific PCR and a prior version of the CYP450 GeneChip assay in an independent and blind

fashion. The CYP2D6 *3, *4, *6, *7 and *9 alleles demonstrated a high degree of concordance between the CYP450 GeneChip and allele-specific PCR methods (>99% concordance) [7,16]. According to Roche, accuracy and specificity was 100% in samples with normal alleles (100 CYP2D6 samples with one of three alleles, *1, *2 or *35, and 261 CYP2C19 samples homozygous for the wild-type allele, *1) [7]. The overall genotype accuracies for CYP2D6 and CYP2C19 were 99.1 and 100%, respectively, in 422 tested samples. The calculation was also performed with the results tallied for the individual alleles, resulting in an overall analytical sensitivity for CYP2D6 genotype detection of 99.2%, and 100% for CYP2C19 genotype detection [7]. This level of accuracy is primarily due to use of redundant probe tiling on the microarray, which in turn enables the setting of very robust cut-offs, despite the challenges of the CYP2D6 gene (including the presence of highly conserved nonfunctional pseudogenes and a high degree of polymorphic variability [16]).

The correct classification of a specific phenotype may be a much more relevant issue for the clinician. Phenotype accuracy is a complex issue that is influenced by our lack of knowledge and by the subject's race. Starting with the easiest phenotype, the CYP2C19 PM, the AmpliChip CYP450 Test includes the two most important inactive CYP2C19 alleles (*2 and *3). Without entering into the details of the variations of these two alleles in different races, other defective alleles have been found, particularly in Caucasians, but the CYP2C19 accuracy of any system testing for two alleles has been estimated to be over 99.1% for Caucasians [11].

The CYP2D6 PM phenotype has been well studied in Caucasians. Four alleles, *3, *4, *5 and *6, appear to account for most (98%) inactive alleles [17]. The AmpliChip CYP450 Test identifies these four, plus another seven inactive alleles, and the inactive duplication *4xn (a total of 12 inactive alleles; TABLE 1). The accuracy of CYP2D6 PM classification for other races is not as well established. A recent article on a US Mexican–American sample suggested that *4, *5 and *6 appear to account for most inactive alleles [18]. The frequency of PMs in Black Africans and US African–Americans is not completely resolved. In Black African populations, the PM frequency has ranged between 0 and 19% depending on the ethnic group and the phenotyping method studied [19]. The differences in activity of different alleles for different phenotyping probes is a major confounding factor [19]. In a study of US African–Americans using only one phenotyping method, it was proposed that 7.3% (14 out of 193) were CYP2D6 PMs according to their dextromethorphan phenotype, but only two of the 14 had clearly identified null CYP2D6 alleles [20]. More recently, the same group has described that the *36 allele may be associated with lack of CYP2D6 activity [21]. Currently, it is not known if the prevalence of PMs in US African–Americans is closer to the 2% (based on current confirmed null alleles) or to the 7% (based on this small study) [20]. More research is needed to establish whether there are unidentified inactive alleles in US African–Americans or whether dextromethorphan overestimates the prevalence of PMs by including some IMs as incorrectly classified PMs [10]. The possible lack of accuracy for the classification of PMs in US African–Americans is a problem, not only for the AmpliChip CYP450 Test, but for any CYP2D6 genotyping or phenotyping method currently used. Although no large study on East Asians using the AmpliChip CYP450 Test has been published, it is expected that this test should accurately classify CYP2D6 PMs among East Asians.

The IM phenotype and low functioning alleles need more research. A very frequent allele in East Asians, *10, is associated with lower enzyme stability (lower levels) and with a consistent lower level of functioning in metabolizing several CYP2D6 substrates. The AmpliChip measures the *10A, *10B and *10xn alleles. Allele *17, typical of Black subjects, does not appear to be associated with the same uniform level of lower metabolic activity across substrates [22]. Moreover, according to the author's study, *17 appears to be associated with normal, or even higher than normal, metabolic activity for risperidone [10]. The AmpliChip also measures the *17 and *17xn alleles. In summary, the activity of some of the alleles associated with lower CYP2D6 activity may be substrate dependent, and our current knowledge is limited. If the author's data on risperidone and *17 are replicated with other CYP2D6 drugs, this would make the prediction of dosages of CYP2D6 drugs in Black Africans and US African–Americans particularly complicated. The same individual may have decreased activity metabolizing some CYP2D6 substrates, and increased activity metabolizing others.

Our understanding of the CYP2D6 UM phenotype is limited, due to the difficulty in establishing a clear distinction from the EM phenotype, and a lack of information on how to compare the different phenotyping methods for establishing UMs. None of them is a good gold standard. The general agreement is that a genotype displaying a duplication (or multiplication) of one active allele in one chromosome plus a full active allele can be defined as a CYP2D6 UM. A major problem is that only a minority of the subjects that appear to be fast metabolizers (potentially UMs) have duplications; some may have currently unidentified genetic variations. Lovlie and coworkers estimated that only 10–30% of UMs in Caucasian populations have CYP2D6 duplications [23]. In summary, it is possible that current genetic CYP2D6 testing focused solely on duplications may have a great number of false negatives for CYP2D6 UM identification, or it is possible that the phenotyping systems being used are not accurate enough to distinguish between CYP2D6 EMs and UMs. The AmpliChip CYP450 Test identifies duplications of three CYP2D6 active alleles: *1xn, *2xn and *35xn [7,13]. If a duplication of any of these three alleles is associated with an active allele in the other chromosome, the patient is classified as a CYP2D6 UM. The AmpliChip CYP450 Test also identifies the CYP2D6 duplications *4xn, *10xn, *17xn and *41xn: *4xn duplication is associated with no CYP2D6 activity; *10xn and *41xn duplications are associated with reduced CYP2D6 activity; and *17xn duplication may be associated with variable activity depending on

the CYP2D6 substrate. In conclusion, the CYP2D6 UM phenotype is diagnosed when the patient has at least three active alleles, but the patient can have more than three active alleles by having a multiplication in one chromosome. It is thought that the CYP2D6 concentrations in the liver are greater with each additional copy of an active allele. The AmpliChip Test does not identify the number of extra copies; it only indicates that at least three active copies are present. The quantification of the number of copies is a complex process that is not easily extrapolated from research to clinical laboratories; in fact, it is not performed in any of the other CYP2D6 genotyping parallel systems described in this article. It is currently believed that most multiplications involve two tandem genes (duplications), with higher multiple tandem copies being far less prevalent [13]. Assuming the current definition of UM genotyping is correct, the AmpliChip CYP450 should identify all CYP2D6 UMs, which include approximately 5% of the Caucasians in Europe or US European descendants, and 4.5% of US African–Americans [10]. There are no published data on Mexican–Americans or other US Hispanic populations, but it should be expected that CYP2D6 UMs may be more frequent than PMs among them.

As a summary regarding phenotypes, the AmpliChip CYP450 Test has good sensitivity and specificity for CYP2C19 PM phenotypes in all races and CYP2D6 PM phenotypes in Caucasians and most likely in East Asians. Practically all CYP2D6 or CYP2C19 PMs currently identified by the AmpliChip CYP450 Test will continue to be identified as PMs, even if tested some years down the road with more sophisticated versions of this test or other new genotyping systems. Our current knowledge of the identification and the clinical meaning of the distinction of other CYP2D6 phenotypes (IM vs EM, or EM vs UM) is limited. Thus, subjects currently classified by the AmpliChip CYP450 Test (or any other system) as CYP2D6 IMs, EMs or UMs may be reclassified in the future. Possible scenarios are: a current CYP2D6 EM is reclassified as a CYP2D6 UM when more knowledge of genotyping is acquired; or a subject who is currently classified as a CYP2D6 IM is reclassified in the future as an IM for some substrates and an EM for others.

The ability to use the sensitivity and specificity of a phenotype to make clinical predictions may vary from drug to drug; and it is possible that the way medication is prescribed (e.g., dose or co-medications) may also have a dramatic influence on predicting clinical outcome. In the author's study with patients taking risperidone [24], the CYP2D6 PM genotype had low sensitivity (16%), moderate specificity (77%) and high accuracy (94%) in the prediction of clinically relevant adverse drug reactions (ADRs) [12]. By comparison, risperidone therapeutic drug monitoring (TDM) had a little higher sensitivity (25%), lower specificity (61%) and lower accuracy (72%). In the author's study of patients discontinued from risperidone, the CYP2D6 PM genotype had low sensitivity (9%), moderate specificity (63%) and high accuracy (97%) in predicting that the reason for discontinuation was ADRs [12]. The accuracy of risperidone TDM could not be compared in patients previously discontinued from risperidone (risperidone TDM was unavailable).

Table 1. CYP26D6 and CYP2C19 genotyping with AmpliChip CYP450 Test versus Tm Biosciences Tag-It™ Kit.

Parameter	AmpliChip CYP450 Test	Tm Tag-It Kit
Costs		
Platform	Affymetrix GeneChip® 3000 Dx	Luminex xMAP® System
Retail value (US$)	~200,000[1]	~50,000[1]
Other uses	Two oncology tests in development[2]	Can run other genetic tests[3]
Costs per sample		
Retail value (US$)	~400 per chip[1]	<100 per sample[1]
Patient costs (US$)	600–1350[4]	585–622.60[5]
*Wild-type allele (*1) identification*		
CYP2D6	Has a wild-type or mutant sequence for each of 27 alleles[6]	By default after excluding 12 mutant alleles
CYP2C19	Has a wild-type or mutant sequence for each of three alleles[6]	By default after excluding seven mutant alleles
Mutant CYP2D6 alleles		
Inactive	*3, *4, *5, *6, *7, *8, *11, *15, *19, *20 and *40 (as well as *4xn)	3, *4, *5, *6, *7, *8, *11 and*12
Low/other[7]	*10	*10
	*9, *10xn, *29, *36, *41 and *41xn	*9
	*17 and *17xn	*17

Table 1. CYP26D6 and CYP2C19 genotyping with AmpliChip CYP450 Test versus Tm Biosciences Tag-It™ Kit (cont.).

Parameter	AmpliChip CYP450 Test	Tm Tag-It Kit
Normal	*2 and *35	*2
Duplications	Active: *1xn, *2xn, *35xn Inactive: *4xn Low/other activity[7]: *10xn, *17xn and *41xn	Does not distinguish active and inactive duplications[8]
Total number	19 mutant alleles[9], seven duplications and one wild-type	12 mutant alleles[10] and unidentified duplications
Mutant CYP2C19 alleles		
Inactive	*2 and *3	*2, *3, *4, *5, *6, *7 and *8
Phenotype identification		
Method	Uses software[11]	By laboratory personnel
CYP2D6		
Ultrarapid metabolizer	At least three active duplications	Based on duplications (active or not)
Extensive metabolizer	One or two active alleles	Two active alleles
Intermediate metabolizer	One or two low activity alleles	One active allele and others
Poor metabolizer	Two inactive alleles (tests for 12 inactive alleles)	Two inactive alleles (tests for eight inactive alleles)
CYP2C19		
Extensive metabolizer	One or two active alleles	Two active alleles
Intermediate metabolizer	(Not used)	One active allele
Poor metabolizer	Two null alleles (tests for two alleles)	Two null alleles (tests for seven alleles)

[1]These are approximate retail values; the actual sale price is unknown to the author as it is the result of discussion between the company and its customers.
[2]Two genotyping oncology tests are in development: the AmpliChip p53 Test and the AmpliChip Leukemia Test.
[3]According to Luminex Corp.'s website, xMAP technology can be used for a wide range of applications throughout the drug-discovery and diagnostic fields. Other Tag-It genotyping kits produced by Tm Biosciences are for cystic fibrosis, coagulation, the Ashkenazi Jewish panel and the CYP2C9 gene. As described in the text, the CYP2C9 gene is important for warfarin treatment. The Tag-It genotyping kit tests for a null allele (*6) and four deficient alleles (*2, *3, *4 and *5). The wild-type allele (*1) is diagnosed after excluding these five alleles.
[4]As of March 2006, several laboratories can genotype using the AmpliChip CYP450 Test, including the Georgia Esoteric and Molecular Lab, affiliated with the Medical College of Georgia (GA, USA). Prices are not yet quoted on their webpage. According to the information provided to the author, the price for one sample for both genes will be US$600. Three large commercial laboratories, LabCorp (NC, USA), Specialty (CA, USA) and Spectrum (NC, USA), describe the AmpliChip CYP450 Test on their websites, but do not provide a cost description. In an e-mail to the author, Spectrum said, "The list price for the test is about US$600, which is just above Medicare reimbursement." In an e-mail to the author, LabCorp quoted a cost of US$1360. They also described an in-house-developed test for CYP2D6, which is estimated to be US$550 (using Tm Biosciences Tag-It Kit or Third Wave Invader® technology), and US$348 for CYP2C19 (using the PCR method).
[5]As of March 2006, several laboratories, Genelex (WA, USA), Genomas (CT, USA), Mayo (MN, USA) and PG_{XL} Laboratories (KY, USA), can genotype for CYP2D6, CYP2C19 and CYP2C9, using Tm Biosciences Tag-It Kit. A Genelex e-mail informed the author that they currently use PG_{XL} Laboratories for CYP2D6, CYP2C19 and CYP2C9 testing, but they plan to have their own genotyping ready in a few months. Each pharmacogenetic test (CYP2D6, CYP2C19 and CYP2C9) is US$250 or US$500 for the combination of CYP2D6 and CYP2C19. Genomas, affiliated with Hartford Hospital, describes on their website charges of US$300 for any of the three genes (CYP2D6, CYP2C19 and CYP2C9); this will be US$600 for the combination of CYP2D6 and CYP2C19 tests. Mayo Medical Laboratories use Tm Biosciences Tag-It Kit for genotyping (CYP2D6, CYP2C19 and CYP2C9). The author has been informed by e-mail from a Mayo Clinic physician that Mayo Medical Laboratories use additional testing to identify duplications and *2 allele. The author could not find the costs on the Mayo Medical Laboratories website, but an e-mail from a Mayo physician described a standard DNA extraction cost of US$150 plus US$236.30 each for genotyping with CYP2D6, CYP2C19 and CYP2C9. According to the author's understanding, the price for CYP2D6 and CYP2C19 genotyping of one sample would be US$622.60 ($622.60 = $236.30 for CYP2D6 + $236.30 for CYP2C19 + $150 for DNA extraction). PG_{XL} Laboratories, affiliated with the University of Louisville (KY, USA), describes on their website charges of US$350 for the CYP2D6 test, US$305 for the CYP2C19 (or CYP2C9) test, US$200 for additional enzymes and US$35 for DNA isolation. According to the author's understanding, the price for CYP2D6 and CYP2C19 genotyping of one sample would be US$585 (US$585 = US$350 for CYP2D6 + US$200 for additional enzyme + US$35 for DNA extraction).
[6]The AmpliChip CYP450 Test contains wild-type and mutant probe sets for each polymorphism, and thus it does not detect the allele *1 by default. It queries directly for either the wild-type or mutant sequence of polymorphism for all 27 alleles of CYP2D6 and three alleles of CYP2C19.
[7]Allele *10 appears to have consistent very low activity. The alleles *9, *10xn, *29, *36, *41 and *41xn appear to have lower than normal activity. The alleles *17 and *17xn may have low activity for some CYP2D6 substrates and higher activity for others.
[8]This may lead to ultrarapid metabolizer overestimations if the laboratory assumes that all duplications reflect active duplications and that all subjects with duplications are CYP2D6 UMs. The text provides some approximate overestimation estimates based on the author's risperidone study.
[9]The AmpliChip CYP450 Test recognizes 19 CYP2D6 mutant alleles: *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *19, *20, *29, *35, *36, *40 and *41. It recognizes more than one of the variants in four alleles: *2ABD, *4ABDJK, *6ABC and *10AB. For example, the AmpliChip CYP450 test recognizes *2A, *2B and *2D as variants of *2.
[10]The Tm Biosciences kit recognizes 12 CYP2D6 mutant alleles: *2, *3, *4, *5, *6, *7 and *8. It has some single nucleotide polymorphisms that are present in more than one variant: *3AB, *4A-L, *6A-D and *10AB.
[11]Infrequently, the AmpliChip CYP450 Test provides a 'No call'. There are three main reasons for this: low-quality DNA, software problems and unidentified alleles.

Comparison with other parallel genotyping methods

Other DNA microarray platforms are being developed for CYP testing, but none have currently been completely developed or approved by the FDA. The published information on the methods used by non-FDA-approved technologies using parallel testing for CYP2D6 and CYP2C19 is limited.

According to a special report of the Blue Cross and Blue Shield Association [109], other companies developing CYP testing include Tm Bioscience (Tm Tag-It™ Mutation Detection Kit) [110] with the Luminex Corp. microsphere-based universal array genotyping platform [111], Third Wave Technologies, Inc. (Invader® Technology) [112], GE Healthcare (CodeLink™ P450 SNP Bioarray) [113] and Jurilab Ltd (DrugMEt™ Genotyping Test) [114].

The Tm Tag-It Mutation Detection Kit is the only other parallel genotyping test commercially available to test individual patients for CYP2D6 and CYP2C19. It can also be used for CYP2C9 genotyping (TABLE 1). As of March 2006, the literature on Tm Tag-It Mutation Detection is limited to an in-press article using this system to genotype CYP2D6, CYP2C19 and CYP2C9 in a hospital sample [25], and an in-press book chapter [26]. A blinded concordance study using a panel of 141 CYP2D6 genomic DNA samples and another using 125 CYP2C19 samples, which have been independently characterized using established methods, both demonstrated a 100% concordance [26]. The author is aware of four laboratories using the Tm Tag-It Mutation Detection Kit for CYP2D6 and CYP2C19 (TABLE 1) [114–117]. The Tm Tag-It Mutation Detection Kit for CYP2C19 detects the two most frequent CYP2C19 null alleles (*2 and *3) and five other rare null alleles (TABLE 1). It appears to be a good system for detecting CYP2D6 PMs, particularly in Caucasians. Problems include that the Tm Tag-It Mutation Detection Kit identifies the wild-type allele by default after excluding 12 tested mutant alleles, does not include some of the CYP2D6 low-functioning alleles, has no phenotyping software, and does not specify which allele may be duplicated (according to one of the testing laboratories, sometimes a decision can be made due to a skewed signal in the duplicated allele) (TABLE 1). The lack of specification of which allele is duplicated may lead a laboratory to consider all patients with duplications as CYP2D6 UMs. This is not correct. There are no estimations in the literature of how worrisome that overestimation is considered to be. The author has used his risperidone study data genotyped with the AmpliChip CYP450 Test to make approximated estimations. Looking at individuals (physician point of view), among 560 patients, there were 18 UMs (3.2%) with active duplications, but 27 (4.8%) with either active and/or inactive duplications. The overestimation was worse among 93 US African–Americans, since there were five UMs (5.4%) with active duplications, but 11 (11.8%) with either active and/or inactive duplications. The overestimation in 457 Caucasians was from 13 (2.8%) to 16 (3.5%). Looking at alleles (laboratory point of view), 27 (2.4%) of the 1120 alleles were CYP2D6 duplications, but only 20 (1.8%) were active duplications. Less than half (five of 11) of the duplicated alleles were active in the 93 US African–Americans.

Third Wave Molecular Diagnostics uses the Invader system, a homogenous, isothermal, highly specific and robust signal amplification system. The CYP2D6 genotyping test needs both the PCR Invader genotyping assay system and the Invader genomic copy-number assay. The test includes 11 CYP2D6 mutations (*2, *3, *4, *5, *6, *10, *11, *18, *33, *35 and *37) and duplications, but does not allow a determination of which allele is duplicated. In 171 samples, the system provided unambiguous genotypes that yielded a visible PCR product on an agarose gel. The copy-number assay yielded only one equivocal result in 205 samples [27].

The CodeLink Bioarray system is a research tool that tests 110 single nucleotide polymorphisms (SNPs) in nine CYP genes, including CYP2D6 and CYP2C19. The DrugMEt Genotyping Test tests for 27 SNPs in eight drug-metabolizing enzymes and has software to interpret the results. For the CYP2D6 gene, it tests for two rearrangements, the deletion (*5) and the duplication (without describing whether it is functional or not), and 11 alleles (*3, *4, *6, *7, *8, *9, *10, *11, *12, *14 and *17). For the CYP2C19 gene, it tests for the more frequent inactive alleles (*2 and *3) and another five less frequent (*4, *5, *6, *7 and *8). It can also test for CYP2C9.

Other recent attempts to develop CYP2D6 genotyping include pyrosequencing, a nonelectrophoretic real-time DNA-sequencing technology [28], and a less expensive PCR-based strategy that may be more suitable for use in developing countries [29].

Implementation centered on the individual or based on a public health approach

As far as the author knows, there is no published discussion on how the results of genotyping the CYP2D6 gene or any other gene should or will be implemented in the clinical world. As a matter of fact there is an "embarrassing dichotomy between the body of pharmacogenetic knowledge and its clinical applications" [30]. The author can imagine implementation centered on the individual or implementation using a public health approach [12].

Implementation centered on the individual is based on the idea that a CYP2D6 PM has a substantially increased risk of ADRs (three- to six-times greater according to the author's risperidone study [24]). For their own benefit, the patient should carry a card identifying themselves as an unusual subject regarding the response to some medications, and that information should be registered at their pharmacy. The patient will need to alert any unaware physicians about this unusual genotype. In the approach centered on the individual, a physician would order the test when the patient asks for it (e.g., if a family member has an unusual genetic profile) or after having repeated problems with several medications.

The public health approach to implementation may be justified by economic issues [12]. Extreme genotypes may not only be associated with unusual drug responses (treatment failure or side effects), but also with more economic costs. In 2000, the mean estimated cost in the US ambulatory care environment for a drug treatment failure was US$977, the mean estimated cost for an ADR was US$1105, and the combined cost was US$1488. The

overall cost of US drug-related problems was estimated to be US$177.4 billion [31]. Furthermore, a pilot pharmacogenetic study in a psychiatric hospital suggested that CYP2D6 PM and UM subjects may increase hospital costs [32]. If studies demonstrate the cost–effectiveness of genotyping, one can envision a time that hospitals or health organizations will genotype all patients before starting their medications. It is hoped that this may not only decrease individual human suffering, but also reduce costs.

Expert commentary

CYP2D6 genotyping certainly is a prime candidate for the first successful pharmacogenetic testing in the clinical environment. Basic and applied knowledge is sufficiently integrated and advanced to the point that the FDA defines CYP2D6 genotyping as one of two valid biomarkers in pharmacogenetics [103]. By chance, many CYP2D6-dependent drugs are psychiatric drugs; thus, pharmacogenetics may progress faster in psychiatry than in other areas of medicine, but it is difficult to predict which drug will become the first to include pharmacogenetic testing as standard practice. The recently published Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study suggests that the first antipsychotic a psychiatrist prescribes for a patient may not be the best choice for that individual [33]. Therefore, the future of personalized medicine in psychiatry, with better pharmacokinetic and pharmacodynamic genetic testing, could ultimately lead to better clinical outcomes in patients taking antipsychotics. Studies such as the US National Institutes of Health (NIH)-funded CATIE may help clinical researchers to change their focus from the current approach used by pharmaceutical companies, which is to try to find the best drug for the average patient. The average patient may indeed be uncommon [5]. The currently available pharmacogenetic testing simply helps clinicians and selected patients to decide if they should 'not take that drug' or 'take this low or high dose', which is termed safety pharmacogenetics [34]. The future may lead to recommendations that would determine the best drug for a particular patient, which is termed efficacy pharmacogenetics [34].

The CYP2D6 genotype appears to influence risperidone response and the appropriate dose for each patient [24]. Risperidone will soon be sold as a generic in the USA, and is already sold as a generic in some European countries. Thus, one can envision a generic risperidone and CYP2D6 genotyping as a very reasonable and cost-effective choice for a first-line antipsychotic. To support this approach, a prospective randomized study is needed to explore whether the CYP2D6 genotype can be used to determine individualized risperidone doses. CYP2D6 PMs probably need half of the standard risperidone dosage, while CYP2D6 UMs with three active alleles may need twice the dosage. Currently, it is not easy to find funding for this type of study, since pharmaceutical companies are not interested in promoting personalized prescription and the NIH has very limited interest in studies using real-world conditions (see 'Key issues').

Thus, the author believes that the use of genotyping to recommend doses should be the first priority. However, the FDA appears to believe that the first pharmacogenetic testing will be to individualize drug selection or detect contraindications, while attempts to recommend dosages will need more validation in controlled settings [1]. This FDA position does not consider the fact that pharmaceutical companies are opposed to adding pharmacogenetic testing to their drugs (see 'Key issues'), and if pharmacogenetic testing reduces the number of patients available to take a drug, that pill will be harder to swallow for a pharmaceutical company than if pharmacogenetic testing only suggests a dosage modification for its drug.

Five-year view

Personalized medicine is not the equivalent of pharmacogenetic testing; some currently available personalized medicine tests in oncology do not involve genotyping. Oncology is fortunate to have the availability of tissue samples from tumor cells, which enables testing for very specific drug targets (proteins expressed) within the tumor cells and the use of monoclonal antibodies. This has led to specific treatments. The first is trastuzumab (Herceptin®), a humanized monoclonal antibody specific to Her2/neu, which has revolutionized the management of metastatic Her2/neu-overexpressing breast cancers [35]. It is not a typical pharmacogenetic test, but can be considered a form of personalized prescription; the treatment is selected according to the gene expression of the cancer in that specific patient. It can be measured in different ways, such as using immunohistochemistry to quantify the number of cell surface receptors, or using a fluorescent *in situ* hybridization assay to quantify the number of genes. Irinotecan is a drug used to treat colorectal cancer. A glucuronidation enzyme, UDP-glucuronosyltransferase (UGT)1A1, is a polymorphic enzyme that plays a role in the detoxification of irinotecan active metabolite. In August 2005, the FDA approved the Invader UGT1A1 Assay by Third Wave Technologies, Inc. [119], the first UGT1A1 pharmacogenetic test, and recommended lower doses of the drug according to the genotype.

In November 2005, the FDA Clinical Pharmacology Subcommittee of the Advisory Committee on Pharmaceutical Sciences recommended that patients taking warfarin have pharmacogenetic testing for two polymorphic genes, *CYP2C9* and vitamin K epoxide reductase complex 1. Before this FDA discussion, it was argued that moving CYP2C9 genotyping forward would require cost–effectiveness studies in patients taking warfarin, the most important CYP2C9 drug [36].

On the other hand, it should be noted that some pharmacogenetic tests do not currently involve genotyping. According to the FDA, thiopurine *S*-methyltranseferase (TPMT) is another valid biomarker [120]. Although the number of subjects with low TPMT activity is low (<5% in Caucasians), leading hospitals treating children with childhood leukemia routinely phenotype by measuring the individual's TPMT activity before starting treatment with mercaptopurine. This is not a genetic test, but a phenotypic test measuring red blood cell enzyme activity [37]. The transition from this TPMT phenotyping test to a genotyping test may be difficult due to the scarcity of drugs this metabolic enzyme metabolizes; besides mercaptopurine, they include thioguanine for some leukemias and azathiopurine, an immunosuppressive agent.

In the next 5 years, personalized medicine tests (whether genotyping and/or microarrays are included or not) will continue to progress in oncology. Oncology benefits from being a specialty that treats lethal diseases with very toxic and expensive medications, and that is practiced by highly specialized physicians. This makes oncology an ideal place to implement personalized medicine and/or pharmacogenetic testing. These same insular characteristics of oncology make it difficult to know if this wave of personalized medicine in oncology will extend to medicine in general. Oncology drugs are not used by generalist physicians; but generalist physicians frequently use psychiatric medications. Therefore, CYP2D6 and CYP2C19 genotyping may hold the possibility of more generalized use than tests developed for oncology. It is not known which pharmacogenetic CYP2D6 and CYP2C19 testing will prevail in the next 5 years. However, it is fascinating that, with the FDA's approval of the AmpliChip CYP450 Test, psychiatry can become a leading specialty in the implementation of pharmacogenetics in general medicine. CYP2D6 and CYP2C19 genotyping must be widely used in psychiatry and better understood in the clinical environment before we can predict what is next. Moreover, there are major obstacles to wide implementation of pharmacogenetic testing in the clinical environment (see 'Key issues').

Disclosure

Roche Molecular Systems, Inc. markets the AmpliChip CYP450 Test detecting the CYP2D6 and CYP2C19 gene variations. Roche Molecular Systems, Inc. supported four of Jose de Leon's lectures, some equipment for his laboratory and an ongoing research-initiated grant. Jose de Leon has not received any consultant payments and has no other financial arrangements with Roche Molecular Systems, Inc. He has no stocks in Roche or Affymetrix. Additionally, in the past 2 years, Jose de Leon has been on the advisory board of Bristol-Myers Squibb; received researcher-initiated grants from Eli Lilly; and lectured supported by Eli Lilly (once) and by Bristol-Myers Squibb (once).

Key issues

Science and technology are ready to introduce cytochrome P450 (CYP)2D6 and CYP2C19 as the first wave of using pharmacogenetic testing for personalizing prescriptions in medicine. These key issues represent the obstacles to this introduction:

- Pharmaceutical companies have no positive incentives for incorporating pharmacogenetic testing of old drugs. For new drugs, the pharmaceutical companies' distrust of pharmacogenetics appears to be leading to: eliminating drugs metabolized mainly by CYP2D6 as marketing candidates [12,38]; and taking a stance that can kindly be defined as 'wait and see', or perhaps better as, 'we do not want to take the risk of being first'. It appears that only enforcement by government agencies may be able to expedite the use of pharmacogenetic testing [39].
- There are obstacles in conducting and publishing pharmacogenetic studies in the 'dirty' real world, which are related to the nonwelcoming attitudes of grant agencies [12,38], pharmaceutical companies [12,38] and scientific reviewers [12].
- Extensive clinical applications may be compromised by economic factors. Cost–effectiveness studies are needed [40].
- Once the pharmacogenetic test is on the market, extensive clinician education will be needed. Published CYP2D6 and CYP2C19 pharmacogenetic guidelines are needed to orient clinicians, including psychiatrists [5,8].
- The US healthcare system is so fragmented that it complicates the use of an implementation based on a public health approach, but, due to its openness to new biomedical advances and its emphasis on quality improvement, implementation centered on the individual and promoted by the US FDA and/or patients and families may be successful.

References

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

1 Harper CC, Philip R, Rabinowitz M, Gutman SI. FDA perspectives in genetic testing. *Expert Rev. Mol. Diagn.* 5, 643–648 (2005).

2 Cappell K, Arndt M, Carey J. Drugs get smart. *Business Week* 5, 76–85 (2005).

3 Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functionary diversity. *Pharmacogenomics J.* 5, 6–13 (2005).
•• Recent summary of the cytochrome P450 (CYP)2D6 gene.

4 Madan A, Graham RA, Carroll KM *et al.* Effects of prototypical microsomal enzyme inducers on cytochrome P450 expression in cultured human hepatocytes. *Drug Metab. Dispos.* 31, 421–431 (2003).

5 de Leon J, Armstrong SC, Cozza KL. Clinical guidelines for using pharmacogenetic testing of CYP450 2D6 and CYP450 2C19 in psychiatry. *Psychosomatics* 47, 75–85 (2006).
• First limited attempt to provide drug dosing guidelines according to CYP2D6 and CYP2C19 genotypes.

6 Chou WH, Yan FX, Robbins-Weilert DK *et al.* Comparison of two CYP2D6 genotyping methods and assessments of genotype–phenotype relationships. *Clin. Chem.* 49, 542–551 (2003).

7 Roche Molecular Systems, Inc. *AmpliChip CYP450 Test for In Vitro Diagnostic Use.* Roche Molecular Systems, Inc., NJ, USA (2005).
• Technical description of the AmpliChip CYP450, equivalent to a package insert for a drug approved by the US FDA. As with package inserts, the author hopes that the FDA will consider an easier-to-read version in the future.

8 Kirchheiner J, Nickchen K, Bauer M *et al.* Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol. Psychiatry* 9, 442–473 (2004).
• Attempt to guide pharmacogenetics based on pharmacokinetic knowledge of psychiatric drugs.

9 Koch WH. Technology platforms for pharmacogenomic diagnostic assays. *Nature Rev. Drug Discov.* 3, 749–761 (2004).

10 Cai WM, Nikoloff DM, Pan RM *et al.* CYP2D6 genetic variations in healthy adults in psychiatric African–American subjects: implications for clinical practice and genetic testing. *Pharmacogenomics J.* (2006) (In Press).

11 Wedlund PJ. The CYP2C19 enzyme polymorphism. *Pharmacology* 6, 174–185 (2000).

12 de Leon J, Susce MT, Murray-Carmichael E. The AmpliChip CYP450 genotyping test: integrating a new clinical tool. *Mol. Diagn. Ther.* (2006) (In Press).

13 Koch WH, Wu L. Genotyping of polymorphic CYP450 genes using the AmpliChip CYP450 test. In: *Pharmacogenomics and Proteomics: Enabling the Practice of Personalized Medicine.* Wong SHY, Linder MW, Valdes R Jr (Eds), AACC Press, DC, USA (2006) (In Press).

14 The Medical Letter. AmpliChip CYP450 Test. *Med. Lett. Drugs Ther.* 47(1215–1216), 71–72 (2005).

15 Greenhalgh T. Papers that report diagnostic or screening tests. *Br. Med. J.* 315, 540–543, (1997).

16 Wu L, Williams M, Koch W. Clinical applications of microarray-based diagnostics tests. *Biotechniques* 39, 577–582 (2005).

17 Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. *Pharmacogenomics* 3, 229–243 (2002).

18 Luo HR, Gaedigk A, Aloumanis V, Wan YJY. Identification of CYP2D6 impaired functional alleles in Mexican–Americans. *Eur. J. Clin. Pharmacol.* 61, 797–802 (2005).

19 Xie HG, Kim RB, Wood AJ, Stein CM. Molecular basis of ethnic differences in drug disposition and response. *Ann. Rev. Pharmacol. Toxicol.* 41, 815–850 (2001).

20 Gaedigk A, Bradford LD, Marcucci KA *et al.* Unique CYP2D6 activity distribution and genotype–phenotype discordance in black Americans. *Clin. Pharmacol. Ther.* 72, 76–89 (2002).

21 Gaedigk A, Bradford LD, Alander SW, Leeder JS. CYP2D6*36 gene arrangements within the CYP2D6 locus: association of CYP2D6*36 with poor metabolizer status. *Drug Metab. Dispos.* 34(4), 563–569 (2006).

22 Wennerholm A, Dandara C, Sayi J *et al.* The African-specific CYP2D6*17 allele encodes an enzyme with changed substrate specificity. *Clin. Pharmacol. Ther.* 71, 77–88 (2002).

23 Lovlie R, Daly AK, Matre GE, Molven A, Steen VM. Polymorphisms in CYP2D6 duplication-negative individuals with the ultrarapid metabolizer phenotype: a role for the CYP2D6*35 allele in ultrarapid metabolism? *Pharmacogenetics* 11, 45–55 (2001).

24 de Leon J, Susce MT, Pan R-M *et al.* The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. *J. Clin. Psychiatry* 66, 15–27 (2005).

• First clinical study using the AmpliChip CYP450 Test in the clinical environment.

25 Ruaño G, Makowski G, Windemuth A *et al.* High carrier prevalence of deficient and null alleles of CYP2 genes in a major USA hospital: implications for personalized drug safety. *Personalized Med.* 3(2), 131–137 (2006).

26 Gordon J, Merante F, Weiss SM *et al.* Pharmacogenetic P450 screening using the Tag-It™ universal bead-based array platform. In: *Pharmacogenomics and Proteomics: Enabling the Practice of Personalized Medicine.* Wong SHY, Linder MW, Valdes R Jr (Eds), AACC Press, DC (2006) (In Press).

27 Neville M, Selzer R, Aizenstein B *et al.* Characterization of cytochrome P450 2D6 alleles using the Invader technology. *Biotechniques* 32, S34–S43 (2002).

28 Söderbäck E, Zackrisson AL, Lindblom L, Alderborn A. Determination of CYP2D6 gene copy number by pyrosequencing. *Clin. Chem.* 51, 522–531 (2005).

29 Dorado P, Caceres MC, Pozo-Guisado E, Wong ML, Licinio J, Llerena A. Development of a PCR-based strategy for CYP2D6 genotyping including gene multiplication of worldwide potential use. *Biotechniques* 39, 571–574 (2005).

30 Ruaño G. *Quo vadis* personalized medicine. *Personalized Med.* 1, 1–7 (2004).

31 Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J. Am. Pharm. Assoc.* 41, 192–199 (2001).

• Thoughtful consideration of the cost issues underlying pharmacogenetic testing.

32 Chou WH, Yan FX, de Leon J *et al.* An extension of a pilot study: impact from the cytochrome P450-2D6 (CYP2D6) polymorphism on outcome and costs in severe mental illness. *J. Clin. Psychopharmacol.* 20, 246–251 (2000).

33 Lieberman JA, Stroup TS, McEvoy JP *et al.* Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N. Eng. J. Med.* 353, 1209–1223 (2005).

34 Roses AD. Pharmacogenetics and drug development: the path to safer and more effective drugs. *Nature Rev. Genet.* 5, 645–656 (2004).

•• Good pharmacogenetics review from one working in a pharmaceutical company.

35 Emens LA. Trastuzumab: targeted therapy for the management of HER-2/neu-overexpressing metastatic breast cancer. *Am. J. Ther.* 12, 243–253 (2005).

36 Kirchheiner J, Brockmoller J. Clinical consequences of cytochrome P450 2C9 polymorphisms. *Clin. Pharmacol. Ther.* 77, 1–16 (2005).

37 Corominas H, Baiget M. Clinical utility of thiopurine *S*-methyltransferase genotyping. *Am. J. Pharmacogenomics* 4, 1–8 (2004).

38 Weinshilboum R, Wang L. Pharmacogenomics: bench to bedside. *Nature Rev. Drug Discov.* 3, 739–748 (2004).

39 Danzon P, Towse A. The economics of gene therapy and of pharmacogenetics. *Value Health* 5, 5–13 (2002).

• Thoughtful consideration of pharmacogenetic testing costs.

40 Wedlund PJ, de Leon J. Pharmacogenetic testing: the cost factor. *Pharmacogenomics J.* 1, 171–174 (2001).

Websites

101 Roche: producer of the AmpliChip CYP450 Test www.roche-diagnostics.com/products_services/amplichip_cyp450.html (Viewed March 2006)

102 Affymetrix: producer of the GeneChip® System 3000Dx Microarray Platform www.affymetrix.com/products/application/clinical_applications.affx (Viewed March 2006)

103 CYP Allele Nomenclature Committee www.imm.ki.se/CYPalleles/cyp2d6.htm (Viewed September 2005)

104 Oragene DNA Self-Collection Kit, which uses saliva www.dnagenotek.com/product.htm (Viewed March 2006)

105 Georgia Esoteric and Molecular Lab: offer CYP2D6 and CYP2C19 genotyping using the AmpliChip CYP450 Test www.gamolecularlab.com (Viewed March 2006)

106 LabCorp: offers CYP2D6 and CYP2C19 genotyping using the AmpliChip CYP450 Test
www.labcorp.com/datasets/labcorp/html/chapter/mono/nf10006770.htm
(Viewed March 2006)

107 Specialty Laboratories: offers CYP2D6 and CYP2C19 genotyping using the AmpliChip CYP450 Test
www.specialtylabs.com/tests/details.asp?id=4565
(Viewed March 2006)

108 Spectrum Laboratories: offers CYP2D6 and CYP2C19 genotyping using the AmpliChip CYP450 Test
www.spectrumlab.org
(Viewed March 2006)

109 Blue Cross and Blue Shield Association. Special report: genotyping for cytochrome P450 polymorphisms to determine drug-metabolizer status. Technical Assessment Program, Volume 19, No. 9, December 2004
www.bcbs.com/tec/vol19/19_09.pdf
(Viewed September 2005)

110 Tm Bioscience: producer of Tag-It™ mutation detection kits
www.tmbioscience.com
(Viewed March 2006)

111 Luminex Corp.: manufacturer of microsphere-based universal array genotyping platform (xMAP® technology)
www.luminexcorp.com
(Viewed March 2006)

112 Third Wave Molecular Diagnostics: producer of the Invader® Technology (the CYP2D6 genotyping test is not presently listed under current products)
www.tmt.com
(Viewed March 2006)

113 CodeLink™ P450 SNP Bioarray (cannot be used for clinical purposes)
www5.amershambiosciences.com/aptrix/upp01077.nsf/Content/Products?OpenDocument&parentid=25670071&moduleid=165695
(Viewed March 2006)

114 DrugMEt™ (described as for research use only)
www.jurilab.com
(Viewed March 2006)

115 Genelex: offers CYP2D6, CYP2C19 and CYP2C9 genotyping using the Tm Tag-It™ Mutation Detection Kit
www.genelex.com
(Viewed March 2006)

116 Genomas: offers CYP2D6, CYP2C19 and CYP2C9 genotyping using the Tm Tag-It™ Mutation Detection Kit
www.genomas.net/lph/forms/hlth_insurance_abn.pdf
(Viewed March 2006)

117 Mayo Medical Laboratories: offers CYP2D6, CYP2C19 and CYP2C9 genotyping using the Tm Tag-It™ Mutation Detection Kit. Additional tests are performed for some CYP2D6 alleles
www.mayoreferenceservices.org/mml/index.asp
(Viewed March 2006)

118 PG_{XL} Laboratories: offer CYP2D6, CYP2C19 and CYP2C9 genotyping using the Tm Tag-It™ Mutation Detection Kit
www.pgxlab.com
(Viewed March 2006)

119 US FDA clears genetic test that advances personalized medicine and helps determine safety of drug therapy
www.fda.gov/bbs/topics/NEWS/2005/NEW012220.html
(Viewed September 2005)

120 US Department of Health and Human Services. Guidance for industry: pharmacogenomic data submission
www.fda.gov/cder/genomics/whatsnew.htm
(Viewed April 2006)

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